The Examiner noted that, on page 13 of the specification, Applicant replaced Table 1 to correct the headings for each column in Table 1, as they appeared to be out of alignment. In an effort to fix the misalignment of those headings, Applicant inadvertently omitted "plus IL-6" in the second line of Table 1. Applicant has amended Table 1 herein to reinsert "plus IL-6"which was inadvertently omitted. As the phrase "plus IL-6" was in the application as originally filed, no new matter has been added by this amendment.

The Examiner objected to Applicant's Abstract of the Disclosure on the grounds that Applicant's use of the phrase "in the absence of antigen" purportedly introduced new matter. The original specification, however, supports this terminology. Applicant's use of the phrase "in the absence of antigen" is supported in the original specification in several locations -- "antigen independent method for the activation of T cells" (Specification at page 2, lines 5-6, and page 3, line 1); and, "T cells can be activated . . . without the problems associated with antigen dependent activation" (Specification at page 4, lines 3-7). Accordingly, it is not new matter under 35 U.S.C. §132. Nonetheless, Applicant has amended the Abstract herein to replace "in the absence" with "independent." Support for this amendment is set forth above. The amended Abstract is also submitted herewith on a separate sheet of paper (Attachment A).

Applicant notes with appreciation the withdrawal of the claim objections.

Rejections Under 35 U.S.C. § 112, second paragraph

The Examiner rejected claims 5 and 6 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that

Applicant regards as the invention. Applicant respectfully traverses this rejection, as those skilled in the art can understand what is claimed when the claims are read in light of the specification.

The Examiner stated that it is unclear as to what the recited dosages therein refer - - i.e., whether. the concentration refers to upon or after administration. Clearly, it means upon administration. It is well settled that, the proper inquiry into whether a claim satisfies the requirement of 35 U.S.C. § 112, second paragraph, is "whether those skilled in the art would understand what is claimed when the claim is read **in light of the specification**." *See Orthokinetics Inc. v. Safety Travel Chairs, Inc.*, 1 U.S.P.Q.2d 1081, 1088 (Fed. Cir. 1986) (emphasis added). Applicant respectfully submits that those skilled in the art can understand what is claimed when the claims are read in light of the specification. As support, the Examiner is directed to the specification at page 10, lines 11-25

Applicant requests that this rejection be withdrawn.

Rejections under 35 U.S.C. § 102(b) and (e)

Claims 1, 3-6 and 10-12 were rejected under 35 U.S.C. § 102(b) as allegedly being anticipated by Chong, U.S. Patent No. 4,879,111. Claims 1, 3-6 and 10-12 were rejected under 35 U.S.C. § 102(e) as allegedly being anticipated by Zimmerman et al., U.S. Patent No. 5,425,940.

The Examiner contends that Chong and Zimmerman disclose administration of a combination of IL-2 and TNF-alpha for treatment of infections and tumors, respectively. The Examiner also argues that the dosages disclosed in Chong and Zimmerman are comparable to the dosages recited in claims 5 and 6. Further, even though the claims recite "antigen independent activation of T cells," the Examiner contends this term does not distinguish Applicant's invention

over the prior art methods, as any effects of IL-2 and TNF-alpha on T cells would be inherent to the prior art methods.

To anticipate a claim, a prior art reference must disclose every feature of the claimed invention, either explicitly or inherently. *Glaxo v. Novopharm, Ltd.*, 334 USPQ2d 1565 (Fed. Cir. 1995). Inherency, however, may not be established by probabilities or possibilities; nor is the mere fact that a certain thing may result from a given set of circumstances sufficient to establish inherency. *See Continental Can Co., U.S.A. v, Monsanto Co.*, 948 F.2d 1264, 1269, 20 U.S.P.Q. 2d 1746, 1749 (Fed. Cir. 1991); *In re Rijckaert*, 9 F.3d 1531, 1534, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) ("The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic"). To reasonably support a determination that an allegedly inherent characteristic *necessarily* flows from the teachings of the cited prior art, the Examiner must provide a basis in fact and/or technical reasoning. *Ex parte Levy*, 17 U.S.P.Q.2d 1461, 1464 (Bd. Pat. App. & Inter. 1990). The Examiner, however, has not provided objective evidence or cogent rationale to support a finding of inherency.

Neither Chong nor Zimmerman disclose "antigen independent activation of T cells." The results reported in Zimmerman, strongly suggest that Zimmerman requires that antigen be present, *e.g.*, by way of "tumor implantation," prior to the administration of any mixture of TNF and/or IL-2 (Chong, Col 11, line12 through Col. 14, line 60). In most cases, the administration of TNF and/or IL-2 was given one day after the host received a tumor cell injection. In fact, Zimmerman requires that the dosage of TNF and/or IL-2 be given within 5-7 days "after the tumor is visible" (See Zimmerman, et al., Col. 4, lines 43-47). Similarly, the method disclosed in Chong requires the

presence of antigen. Chong is directed to "administration to the host of the lymphokine(s), either before or after **infection**" (Chong, Col. 4, lines 38-40), i.e. either before or after antigens present themselves. Accordingly, the timing of the introduction of antigen is important in Chong. For instance, according to Chong the host is to be infected within 18 hours of the lymphokine injection (Chong, Col. 4, lines 45-49). Indeed, when the combination of lymphokines is TNF and IL-2, it is required that the host be injected with the infection 4 hours after the host is injected with TNF (0.01 μg) and IL-2 (10,000 units) (Chong, Col. 11, lines 12-22). Applicant also notes that the concentrations of IL-2 in the present invention (100- 400 U/ml and 200- 300 U/ml) are considerably different from those described in column 5 of Chong (15,000-30,000 units) and column 6 of Zimmerman (15,000-15 million units).

Furthermore, the Applicant's claims do not require, *inter alia*, that TNF and IL-2 be administered in synergistically effective amounts, as defined by Chong and Zimmerman, et al. Applicants therefore request that these rejections be withdrawn.

Rejection under obviousness-type double patenting

Claims 1 and 3-6 and claim 12 were rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1-6 of U.S. Patent No. 6,074,635 ("the '635 patent"). Claims 1-6 of the '635 patent recite *in vitro* methods, whereas the present claims recite *in vivo* methods. The Examiner has not provided any evidence that one skilled in the art would have been motivated to use the taught methods in the '635 patent *in vivo*. much less that they would have a reasonable expectation of success. Nor has the Examiner provided evidence that one of ordinary skill in the art would have been motivated to recognize that treatment

could be effected without manipulating the cells *ex vivo*. Nonetheless, accompanying the filing of this response is the filing of a terminal disclaimer in accordance with 37 C.F.R. 1.321(c), therby obviating the rejection under the judicially created doctrine of obviousness-type double patenting.

Applicant reserves the right to respond to rejections over the prior art made of record, but not relied upon, at such time as they are raised.

New Rejections

Rejections under 35 U.S.C. §112. first paragraph

The Examiner rejected claims 1, 3-6 and 10-12 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification so as to reasonably convey to one skilled in the art that Applicant had possession of the claimed invention at the time the application was filed. The Examiner contends that the specification, as originally filed, does not support Applicant's use of the term "in the absence of antigen" in claim 1. The original specification, however, supports this terminology, and thus the phrase does not change the scope of the disclosure. Accordingly, it is not new matter under 35 U.S.C. §132.

Applicant acknowledges and appreciates the Examiner's invitation to provide evidence of support for the term "in the absence of antigen" in the original specification. Applicant's use of the phrase "in the absence of antigen" is supported in the original specification in several locations, including, for example, the specification at page 1, lines 5-6, ("antigen independent method for the activation of T cells") and the specification at page 4, lines 3-7 ("T cells can be activated . . . without the problems associated with antigen dependent activation"). Applicant's

use of the phrase "in the absence of antigen" in claim 1 is appropriate and supported in the original specification. Thus, the claimed invention does not constitute new matter. Nonetheless, Applicant has amended claim 1 to replace "in the absence" with "independent."

The Examiner rejected claim 10 under 35 U.S.C. 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter that Applicant regards as the invention, as claim 10 depends upon claim 9, which was canceled in Paper No. 6. Applicant has amended claim 10 to replace the reference to claim 9 with "in the preceding claims." This rejection is therefore obviated by Applicant's amendment to claim 10.

The foregoing represents a *bona fide* attempt to advance the present case to allowance. Applicant requests an early notification of the same. If the Examiner feels a telephonic interview would be beneficial, the Examiner is requested to call the undersigned at (215) 564-8352.

Respectfully submitted,

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Dated: September 24, 2001

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VERSIONS WITH MARKINGS TO SHOW CHANGES MADE

In the claims:

1. (twice amended) A method for antigen independent activation of T cells, *in vivo*, comprising contacting T cells [in the absence] independent of antigen with a combination of at least two cytokines selected from the group consisting of interleukin-2, interleukin-6, and tumor necrosis factor alpha, or functionally equivalent fragments thereof.

10. (amended) The method of [claim 9] any of the preceding claims, wherein the activation of the T cells *in vivo* leads to an enhanced immunological response.

In the Abstract:

Please replace the Abstract on page 23 with the following paragraph:

Methods for activating T cells [in the absence] independent of antigen, and compositions effecting the same, are described.

In the Specification:

On page 13, please replace Table 1 with the following table --

	IgM	IgG	IA
B cells cocultured with: IL-2 plus TNF-α plus IL-6	<15	<5	<10
T cells plus medium	<15	<5	<10
T cells plus IL-2	<15	<5	<10
T cells plus IL-2 plus TNF-α	32	23	<10
T cells plus IL-2 plus IL-6	<15	31	28
T-cells plus IL-2 plus TNF-α plus IL-6	75	274	308
T cells plus anti-CD3 mAb plus Il-2	235	219	413

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